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Wolbachia, a bacterium fighting on our side

Studies on the introduction of wolbachia-infected mosquitoes to reduce arboviral infection transmission continue to show great promise. Talha Burki reports.



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When Scott O'Neill started trying to infect *Aedes aegypti* with the *Wolbachia* species bacteria, the intention was to shorten the mosquito's life-span. *Wolbachia* had been known since 1924, when it was discovered living within the common house mosquito, *Culex pipiens*. Experts reckon that well over half of all insect species carry the microbe. In the early 1970s, it was shown that *wolbachia* could colonise an entire population of *Culex* within a few generations, thanks to a property known as cytoplasmic incompatibility. If a male mosquito infected with *wolbachia* mates with an uninfected female, the eggs will not hatch. If an infected female mates with an uninfected male, the offspring will be infected, as will be the case if both parents are infected.

O'Neill, who is now director of the World Malaria Program, had started working on dengue and *wolbachia* in 1980. In 1997, he learned of a strain of *wolbachia* that reproduced fast over time in the cells of infected fruit flies. The strain was named "popcorn", after the appearance of the heavily infected cells. It was deadly to its host. O'Neill wondered whether infecting *A. aegypti* with the "popcorn" strain would kill the mosquito before it was able to transmit dengue virus.

A. aegypti is not naturally infected by *wolbachia* (nor are *Anopheles* spp) so O'Neill's team had to do it themselves. Since the idea was for the bacteria to be passed from generation to generation, the team attempted to infect *A. aegypti* eggs. For this daunting task, one needs a large needle and a very steady hand. In 2006, after thousands of failed attempts, one of O'Neill's students finally succeeded. The bacteria ended

up killing its host much too quickly to be a sustainable means of disease control. But within a couple of years another avenue had opened up.

"In 2008, there was the discovery that *wolbachia* stops viruses from growing in mosquitoes", O'Neill told *The Lancet Infectious Diseases*. The bacteria blocks a whole range of RNA viruses, including chikungunya virus, dengue virus, yellow fever virus, and Zika virus. The "popcorn" strain was not needed after all; the infection with *wolbachia* was enough. O'Neill settled on a less virulent strain called wMel.

After almost three decades of relatively sedate progress, things started to move rapidly. In 2011, O'Neill started field trials in northern Australia, an area not endemic for dengue but with some local transmission. *A. aegypti* is not a particularly mobile insect, so the investigators released a handful of *wolbachia*-infected mosquitoes every 50 m or so. Within weeks, virtually all the mosquitoes in the area carried *wolbachia*. From 2011–2019, hundreds of thousands of *wolbachia*-infected mosquitoes settled in northern Australia.

Risk assessments have concluded that the bacteria is safe, a point borne out by its proliferation in the insect community, without causing any documented harm to human beings. The World Mosquito Program oversees international disease control efforts using *wolbachia*. It currently has projects operating in 12 countries. As of December 2019, *wolbachia*-infected mosquitoes had colonised areas with a population of five million people. The initial results are encouraging. In Vinh Luong in Vietnam, for example, where the releases were completed in 2018 over

an area of 2.2 km², there has been a reduction in dengue incidence of 86%, compared to a neighbouring city with no release of mosquitoes.

Wolbachia-carrying mosquitoes have been released over an area of 18.4 km² in the city of Yogyakarta in Indonesia. This is the site of the first randomised controlled trial involving *wolbachia*. A pilot study found that dengue incidence had dropped by 76% in the areas where the infected mosquitoes were released. "It is looking very positive", said O'Neill, who is an investigator on the randomised controlled trial. "We are expecting to see a very significant impact on transmission in an endemic area with heavy transmission." The study will compare the number of cases of dengue in clusters within the city where the infected mosquitoes have been released with the number of cases in clusters where there have been no releases. Results are expected sometime within the next couple of months.

"The randomised controlled trial will give us the gold standard evidence that we require", said Luciano Moreira (Fundação Oswaldo Cruz, Rio de Janeiro, Brazil). Since the beginning of 2019, Brazil has reported over 3 million cases of dengue. The country has previously been badly affected by chikungunya and Zika, as well as yellow fever, though unlike in Africa this does not appear to be transmitted by *A. aegypti*.

There are ongoing *wolbachia* projects in Rio de Janeiro and Niteroi. Moreira points out that incidence of chikungunya has fallen in areas where the infected mosquitoes have been deployed. Still, it will be tricky to determine the impact of *wolbachia* on Zika and

chikungunya. The two diseases are sporadic and unpredictable, which makes scheduling a trial a difficult proposition. Dengue is far more widespread.

"We collected the wolbachia-carrying mosquitoes in Niteroi two years after they had been released and infected them with dengue and Zika viruses—the virus blocking was still very strong", said Moreira. "That is good evidence that it is working". Wolbachia has several different ways to block viruses from replicating, which makes the emergence of resistance less likely. Elizabeth McGraw's group at Pennsylvania State University has attempted to evolve viruses that are resistant to wolbachia. Thus far, it has proved a difficult task. "Resistance probably will happen eventually, but I do not think it will be a challenge for now", said McGraw. "The important thing is to have a strategy for when resistance does emerge." It is also

conceivable that *A aegypti* could develop resistance to wolbachia or that the cytoplasmic incompatibility could weaken over time.

McGraw believes the major short-term challenges will be deploying the technology over large spaces as well as adapting to local conditions. "Wolbachia will not work perfectly in all places", she said. "There will be interaction between mosquito genotypes and environmental effects such as temperature or local population ecology which might have an effect on the rollout." The wolbachia-carrying mosquitoes are already cross-bred with local mosquitoes for several generations before they are released, so as to ensure they have similar susceptibility to insecticide. Further tweaks to the model may prove necessary over time.

The picture will clarify after the clinical trial results become available, but it is possible that wolbachia could

be turned against other vector-borne diseases, such as malaria. One key consideration is that malaria is transmitted by dozens of different species, whereas *A aegypti* is a single global population. Targeting dengue should certainly have valuable knock-on effects for other diseases, but whether policymakers in Africa will be willing to invest in large-scale dengue elimination efforts, given the scale of the malaria problem on the continent, remains to be seen.

McGraw is highly encouraged by the progress so far. "Wolbachia has continued to surprise researchers in its capacity to do what we want it to do", she told *The Lancet Infectious Diseases*. And in the era of COVID-19, which has forced a halt to vector-control activities, an intervention capable of sustaining itself suddenly seems very valuable.

Talha Burki

Infectious disease surveillance update

Measles in Burundi

Since November 2019, cases of measles have been increasing in Burundi. The cases began in DR Congo refugees staying in the refugee transit camp of Cishemere in Cibitoke health district. The refugees spend 21 days in the transit camp before arriving at their designated permanent camp. The outbreak was identified when cases were being reported in local residents. As of Apr 27, 2020, 857 cases had been reported from four districts: Cibitoke (n=624), Butezi (n=221), Cankuzo (n=6), and South Bujumbura (n=6). The majority of cases were not vaccinated or unsure of their vaccination status (77%).

Dengue in Singapore

As of May 6, 6800 cases of dengue have been reported in Singapore since the beginning of the year. At the

current rate, the cases reported this year could exceed the 16000 cases that were reported in 2019. In response, the National Environmental Agency will expand the release of wolbachia-carrying mosquitoes in endemic areas. Wolbachia-carrying mosquitoes reduce the spread of dengue virus through reducing the ability of the mosquito to transmit the virus to humans.

Polio in Afghanistan

Six cases of wild poliovirus 1 (WPV1) polio have been reported in Afghanistan between April 27 and May 3. Two cases were reported from the Kandahar province and one each from the Badakshan, Balkh, Hirat, and Kunar provinces. The onset of paralysis date for the most recent case was Mar 21. As of May 6, the total number of cases of WPV1 has been 11 this year, while 29 cases were reported in 2019.

Hantavirus in Taiwan

The first case of hantavirus pulmonary syndrome in northern Taiwan has been reported in Keelung in a man in his 40s. The man, who worked in a restaurant, started having symptoms on April 10. According to the Taiwan Centre for disease control, the man was hospitalised on April 11; however, only a second test on April 27 led to confirmation of hantavirus infection. Hantavirus is spread through the faeces, urine, and saliva of infected rodents. The patient reported seeing rats at his workplace, so both the workplace and places he visited were sterilised and pest control was conducted. Four cases of hantavirus infection have been reported across Taiwan so far this year.

Ruth Zwizwai



For more on measles in Burundi see <https://www.who.int/csr/don/06-may-2020-measles-burundi/en/>

For more on dengue in Singapore see <http://outbreaknewstoday.com/singapore-dengue-cases-rise-officials-expand-release-of-wolbachia-carrying-aedes-aegypti-mosquitoes-30836/>

For more on polio in Afghanistan see <https://polioeradication.org/polio-today/polio-now/this-week/>

For more on hantavirus in Taiwan see <https://promedmail.org/promed-post/?id=7308285>